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| Question | |
| **Should absence vs. presence of seizures be used for predicting good neurological outcomes in children following a cardiac arrest?** | |
| **Population:** | Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause. |
| **Intervention:** | Absence of seizures |
| **Comparison:** | presence of seizures |
| **Main outcomes:** | Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2. |
| **Study DESIGN** | Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols\*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created. |
| **TIMEFRAME** | All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th, 2022. |

# Assessment

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| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Most of these deaths occur because of withdrawal of life-sustaining treatment (WLST) based on prediction of unfavorable neurological outcome. Prognostication is of utmost importance because inappropriate WLST can be avoided in those likely to survive with good neurological outcomes. Prediction of favourable neurodevelopmental outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and/or legal guardians. |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know | Twelve studies reported the relationship between absence or presence of seizures in children post-cardiac arrest and good neurological outcomes at PICU/hospital discharge, 6 months, and 12 months [Brooks 2018 324, Ducharme-Crevier 2017 452, Fung 2019 349, Kirschen 2021 e719, Lin 2019 534, Meert 2019 393, Moler 2017 318, Moler 2015 1898, Ostendorf 2016 667, Topjian 2016 547, Yang 2019 223]. These studies included 1165 children, of which 4/12 studies reported using the ACNS criteria [Ducharme-Crevier 2017 452, Fung 2019 349, Ostendorf 2016 667, Yang 2019 223].    Absence of seizures up to 24 hours post-ROC had a sensitivity of 50-100% with a FPR of 63-98% for predicting good neurological outcome at various time points. Absence of seizure after 24 hours had a sensitivity of 50-100% with a FPR of 42-100% for predicting good neurological outcome. |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | A false positive result of EEG may suggest that favorable neurological outcome is likely in patients with an eventually poor neurological outcome. A false positive prediction of a favourable outcome and continued treatment based on absence of seizures on EEG may lead to inappropriate treatment in a patient with an unfavourable neurodevelopmental outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity. |  |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies | The certainty of evidence about seizures was low due to the limited number of studies, very low precision of most studies and the risk of self-fulfilling prophecy. |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability | Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment.  We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest.  A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment.  high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological outcome. |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know | The absence of clinical or electrographic seizure (as defined by American Clinical Neurophysiology Society) was 50-100% sensitive and FPR of >40% for prediction of good neurological outcomes in children post-cardiac arrest. The balance of effects therefore favors against the use of this as a predictive test for good neurological outcome. |  |
| Resources required How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know | We did not include any specific studies assessing costs of assessing seizures on EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in resource-limited settings. |  |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies | We did not identify any studies specifically assessing costs of performing continuous electroencephalography and/or ruling out seizures. |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies | We did not identify any studies addressing cost-effectiveness of seizure detection using continuous electroencephalography after cardiac arrest. |  |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know | The specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity. |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | We have not identified any research that assessed acceptability of clinical or electroencephalographic seizures as a predictor, or that of the American Clinical Neurophysiology Society's definition of electrographic seizures. However, acceptability is likely. |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | Feasibility was not specifically addressed in any of the studies included in this review. Diagnosis of seizures on continuous EEG requires specific equipment for recording EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day. |  |

# Summary of judgements

|  | **Judgement** | | | | | | |
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| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | **Small** | Trivial |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | **Possibly important uncertainty or variability** | Probably no important uncertainty or variability | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | **Probably reduced** | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Type of recommendation

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| Strong recommendation against the intervention | Conditional recommendation against the intervention | **Conditional recommendation for either the intervention or the comparison** | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○ | ○ | **●** | ○ | ○ |

# Conclusions

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| Recommendation |
| We suggest **against** using the absence of clinical or electrographic seizures (as defined by American Clinical Neurophysiology Society) up to 24 hours or later after return of circulation to predict **good** neurological outcome in children after cardiac arrest (weak recommendation, very-low-certainty evidence). |
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| Justification |
| **Overall justification**  For clinical or electrographic seizures, 12 studies suggest that their absence up to 24 hours or beyond 24 hrs post cardiac arrest had a reasonable sensitivity but high FPR for predicting good neurological outcomes.      **Detailed justification**  *Certainty of evidence*  None of the studies adjusted for the confounding effect of sedation or targeted temperature management on the absence of seizures  *Resources required*  Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources.  *Equity*  Resources required for continuous EEG monitoring and interpretation may not be available in resource-limited settings |

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| Subgroup considerations |
| None |

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| Implementation considerations |
| Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings. |

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| Monitoring and evaluation |
| None |

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| Research priorities |
| Evaluation of association between seizure burden during the first 72 hours post cardiac arrest and neurological outcomes is needed.  Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions. |

# References Summary